REMARKS/ARGUMENTS

The application has been amended. In particular, the sequence listing filed November 20, 2002 has been deleted from the specification, and the corrected sequence listing submitted herewith has been added. Also, an amendment to Figure 1 has been made by replacement sheet. Moreover, claims 1, 2, 4, 5-20, 30, 33, 36, 44 and 48-52 have been amended, and claims 42, 43 and 47 have been canceled. Subject matter from canceled claim 47 has been incorporated into claim 44. Support for these amendments can be found in the application as filed. Applicants reserve the right to pursue the canceled claims in a continuation application.

Objections

The Examiner has objected to the disclosure for lacking a description for the figure filed September 20, 2004. Applicants submit that a description for this figure was present in the application as filed. In particular, the brief description of the new figure is located in the paragraph immediately following the heading "Brief Description of Drawing".

The Examiner has also objected to the amendment filed September 20, 2004 for allegedly introducing new matter into the disclosure. In particular, the Examiner is of the opinion that the value of 1.80 for h-collagen I in replacement Figure 1 is new matter, because in Table 1, the absorbance for this protein is given as 1.79. Applicants submit that this does not constitute new matter, since 1.80 in the figure was simply rounded-off from 1.79. However, in an effort to remove any suggestion of a new matter introduction, Applicants have amended Figure 1 by replacement sheet to remove the number 1.80.

Claim rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 4, 30-32, 35, 41 and 47 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner indicates that the elected sequence, HKNQT, is not the same as SEQ ID NO: 34 in the Sequence Listing filed November 20, 2002. It is unclear to the Examiner which sequence was intended by Applicants.

In response to this rejection, Applicants have submitted herewith a corrected sequence listing to correct a typographical error in SEQ ID NO: 34. In particular, SEQ ID NO: 34 has been corrected to read HKNQT, as intended by Applicants. It is noted that this amendment does not constitute new matter, since the intended sequence, HKNQT, was present throughout the specification and claims as filed.

In view of Applicants' submission of the corrected sequence listing, removal of this rejection is respectfully requested.

Nonstatutory Double Patenting Rejections

The Examiner has provisionally rejected claims 1, 2, 4, 6-13, 15, 19, 30-32, 41, 42 and 49-52 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-53 of copending Application No. 10/259,816.

Also, claims 1, 2, 5-17, 19-21, 33, 36, 37, 42-44 and 48 have been provisionally rejected claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-40 of copending Application No. 10/641,286.

Moreover, claims 1, 2, 5-17, 19-21, 33, 36, 37, 42-44 and 48 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-66 of copending Application No. 10/670,771.

The Examiner has also rejected claims 1, 2, 5-7, 10-12, 19 and 42 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 6, 759, 510. The Examiner is of the opinion that, although the conflicting claims are not identical, they are not patentably distinct from each other because the '510 patent

claims SEQ ID NOS: 25, 30, 34, 40, 53-55, 58, 62, 70-72, 79-81 and 86-88, which have the same structure as is recited in the instant claims.

With respect to the double patenting rejections, Applicants will consider the appropriateness of filing a terminal disclaimer upon the finding of allowable subject matter in the present application.

Rejections under 35 U.S.C. §102 (e)

U.S. Patent No. 6, 759, 510

The Examiner has rejected claims 1, 2, 5-7, 10-12, 19, 42, 44 and 48 under 35 U.S.C. §102 (e) as allegedly being anticipated by Applicant's own U.S. Patent No. 6, 759, 510. The Examiner references the above obviousness-type double patenting rejection, where he lists specific peptide species. The Examiner also indicates that the '510 patent teaches the use of the peptides in cell cultures.

Claim 1, as amended, now recites a cell culture system comprising a pentameric peptide, wherein the peptide comprises a pentameric structure of at least one of the generic structures (a)-(e). Regarding situations where generic claims are presented for the first time after issue of species, Applicants refer to MPEP § 806.04(i), which states:

> **The Office no longer follows the practice of prohibiting the allowance of generic claims that are presented for the first time after the issuance of a copending application claims plural species. Instead, the Office may reject the generic claims on the grounds of obviousness-type double patenting. Applicant may overcome such a rejection by filing a terminal disclaimer. See *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967).**

In view of this MPEP rule, Applicants believe that maintaining the 102(e) rejection of claim 1, 2, 5-7, 10-12 and 19 would be improper. Therefore, Applicants respectfully request that these rejections be withdrawn.

Applicants have canceled claim 42, thereby obviated the rejection of this claim. Moreover, claims 44 and 48 have been amended to recite the peptides in original claim 4, thereby obviating the rejection of these claims.

U.S. Patent No. 6,552,249 to Cahoon, et al. (hereinafter, Cahoon)

The Examiner has also rejected claims 1, 2, 4-7, 10-12, 19, 30, 32, 41 and 42 under 35 U.S.C. §102 (e) as allegedly being anticipated by Cahoon. In particular, the Examiner states that Cahoon teaches a soybean cinnamyl-alcohol dehydrogenase polypeptide comprising the sequence HKNQY. He also states that in view of the similarity in structure between this peptide and the instant claimed peptides, the peptide of Cahoon will inherently enhance cell growth and/or secretion, will promote adherence of anchorage-dependent cells, and will increase oxygen consumption to the same extent claimed by Applicants.

Independent claim 1 now recites a cell culture system comprising a pentameric peptide which enhances cell growth and/or secretion, wherein the peptide comprises a pentameric structure of at least one of (a) xxxkx, (b) xxkxx, (c) xxxxk, (d) xkxxx, and (e) kxxxx.

In contrast to the present invention, Cahoon fails to disclose, teach or suggest a pentameric peptide that enhances cell growth and/or secretion. Instead, Cahoon is directed to the isolation and characterization of cDNA clones encoding an enzyme, and to the expression of these cDNAs in cells. The dehydrogenase enzyme is not a pentameric peptide having one of the recited pentameric structures. Rather, it is a whole protein. As stated in the application at page 16, paragraph [0041], whole proteins or large peptides are more likely to be degraded by endogenous and exogenous proteases within a cell culture system. Therefore, the use of whole proteins or large peptides in cell culture systems is not desirable. Moreover, there is no teaching or suggestion in Cahoon to use the dehydrogenase to enhance cell growth and/or secretion as provided by Applicants' invention. The mere possibility that Cahoon's protein possesses such

functional properties is not enough to establish inherency. In order to be inherent, it has to possess such properties.

Regarding independent claims 30 and 41, as noted above, Applicants have filed herewith a substitute sequence listing in order to correct SEQ ID NO: 34. In particular, SEQ ID NO: 34 is HKNQT, as recited in Applicants' original claims. In contrast to the present invention, Cahoon's polypeptides do not correspond to any of the pentameric peptides recited in claims 30 and 41. Furthermore, Cahoon does not disclose or suggest a cell culture substrate including Applicants' recited peptides.

Independent claim 42 has been canceled. Therefore, the rejection of claim 42 is obviated.

In view of the amendments and remarks above, Applicants submit that independent claims 1, 30 and 41 and the claims depending therefrom are patentable over Cahoon. Withdrawal of these rejections is therefore respectfully requested.

U.S. Patent Application Publication 2003/0045476 to Ruoslahti, et al (hereinafter Ruoslahti)

The Examiner has further rejected claims 1, 2, 5-7, 10-12, 16, 18, 19, 42 and 43 under 35 U.S.C. §102 (e) allegedly being anticipated by Ruoslahti. In particular, the examiner states that Ruoslahti teaches a peptide of SEQ ID NO: 10, which comprises a xkxxx structure, linked to VEGF. The Examiner also states that in view of the similarity in structure between Ruoslahti's peptides and the instant claimed peptides, inherently the peptides of Ruoslahti will enhance cell growth and/or secretion in a cell culture system, will promote adherence of anchorage-dependent cells on a surface, and will increase oxygen consumption of cells to the same extent claimed by Applicants.

In contrast to the peptides of Applicants' invention, Ruoslahti's peptide of SEQ ID NO: 10 is not a pentamer. Instead, it is a 12-mer. As noted in Applicants' background in paragraph [0008], disadvantages of using peptides of similar length (e.g., a 13-mer) have been that they are highly susceptible to degradation at high temperatures such as those used during cell culture and to the proteolytic action of the cultured cells themselves. Moreover, Ruoslahti does not disclose or suggest that a functional property of his SEQ ID NO: 10 is to enhance cell growth and/or secretion in a cell culture system, as recited in Applicant's claims. Ruoslahti, at best, teaches a peptide which homes to cardiac tissue, thereby allowing a therapeutic agent to which it is conjugated (e.g., VEGF) to encourage cell proliferation. See, paragraphs [0007], [0019] and [0020]. This is actually a teaching away from the present invention, since it teaches that the therapeutic agent is that which encourages cell proliferation, and not the peptide.

In view of the amendment to claim 1, and the remarks presented herewith, Applicants submit that claim 1, and the claims depending therefrom are patentable over Ruoslahti. Applicants respectfully request withdrawal of these rejections. Claims 42 and 43 have been canceled, thereby obviating these rejections.

Rejections under 35 U.S.C. §102 (b)

U.S. Patent No. 5,411,956 to Miyazaki, et al (hereinafter Miyazaki)

The Examiner has rejected claims 1, 2, 4-7, 10-12, 19, 30, 32, 41, 42 and 49-52 under 35 U.S.C. 102(b) as allegedly being anticipated by Miyazaki. In particular, the Examiner refers to Table 6 and states that Miyazaki teaches the peptide α-(L-lysine)$_5$. He also states that this peptide has the same structure as is recited in instant claims 1, 49 and 50. The Examiner is of the opinion that the peptide of Miyazaki will inherently enhance cell growth and/or secretion in a cell culture system, will promote adherence of anchorage-dependent cells on a surface, and will increase oxygen consumption of cells to the same extent claimed by Applicants.

The results in Table 6 of Myazaki are experimental results from an assay in which various lysine oligomers are being tested for their ability to inhibit enzymatic hydrolysis of lipids present in olive oil. There is no disclosure or suggestion in Myazaki of a cell culture system, as provided in amended claim 1. There is also no disclosure or suggestion in Myazaki of a cell culture substrate, as provided in Applicants' original claim 41 language. Therefore, Applicants submit that product claims 1 and 41, and the depending claims, are not anticipated by the lysine peptides of Miyazaki, nor are they obvious. It is commonly known that there are two basic ways of culturing cells, such as animal cells:

- The cells are immobilized on a substrate and then perfused with culture medium;
- The cells are in a free suspension which is very gently mixed and aerated.

Miyazaki discloses neither of these ways of culturing cells with his peptides. Instead, Miyazaki discloses that his enzyme-inhibiting peptides are useful as a dieting agent for the prevention of obesity and lipemia, and as an additive for food and feed.

Regarding the remaining claims, Applicants have amended claim 30 to delete the peptide, KKKKK, therefrom. Applicants have canceled claims 42 and 43, thereby obviating these rejections. Moreover, amended claims 49 and its depending claims are now directed to a method for enhancing cell secretion in a cell culture system using a peptide possessing all positively charged amino acids.

In view of Applicants' amendments and remarks presented herewith, it is submitted that the claims of the present invention are patentable over Miyazaki. Withdrawal of these rejections is therefore respectfully requested.

U.S. Patent No. 5,955,578 to Pierschbacher, et al. (hereinafter Pierschbacher)

The Examiner has rejected claims 1, 2, 5-17, 19, 42-44 and 48 under 35 U.S.C. §102(b) as allegedly being anticipated by Pierschbacher. In particular, he states that Pierschbacher teaches a matrix comprising peptides comprising an xxxxk structure, conjugated to a biodegradable polymer, such as hyaluronic acid or chondroitin sulfate. He also states that the matrix provides binding sites for cells during wound healing. Moreover, he states that in view of the similarity in structure between the peptides of Pierschbacher and the instant claimed peptides, inherently the peptides of Pierschbacher will enhance cell growth and/or secretion in a cell culture system, will promote adherence of anchorage-dependent cells, and will increase oxygen consumption of cells to the same extent as claimed by Applicants.

As described above, claim 1 as amended is directed to a cell culture system comprising a pentameric peptide which enhances cell growth and/or secretion, wherein the peptide comprises a pentameric structure of at least one of recited structures (a)-(e). Amended claim 1 also recites that the peptide is free or non-covalently immobilized to a cell culture surface.

In contrast to the present invention, Pierschbacher fails to disclose, teach or suggest a pentameric peptide that enhances cell growth and/or secretion. Instead, Pierschbacher discloses a conjugate of a biodegradable polymer and a peptide sequence that is not a pentameric peptide. In column 4, lines 14-24, he discloses that polypeptides that are useful in combination with a biodegradable polymer to promote wound healing include: RRRRRRGDSPK (11-mer); and G(dR)GDSPASSK (10-mer). As described in Applicants' background in paragraph [0008], disadvantages of using peptides of similar length (e.g., a 13-mer) have been that they are highly susceptible to degradation at high temperatures such as those used during cell culture and to the proteolytic action of the cultured cells themselves.

Also, the peptides of Pierschbacher are disclosed as being covalently joined to the biodegradable polymer (column 4, line 65-67 to column 5, lines 1-5). As recited in Applicants'

background, covalently derivatizing peptides to surfaces can present disadvantages in terms of required large concentrations of peptide, the length in time needed for the covalent derivatization, etc.

In view of the amendment to claim 1 and the remarks presented herewith, Applicants submit that claim 1, and the claims depending therefrom are patentable over Pierschbacher.

Regarding the remaining rejections, claims 42 and 43 have been canceled, thereby obviating these rejections. Claims 44 and 48 have been amended to recite the peptides listed in original claim 30, which are not disclosed in Pierschbacher. Therefore, Applicants submit that claims 44 and 48 are also patentable over Pierschbacher.

Therefore, Applicants respectfully request withdrawal of these rejections.

U.S. Patent No. 6,121,027 to Clapper (hereinafter Clapper)

The Examiner has rejected claims 1, 2, 5-13, 15, 19, 33, 42, 44 and 48 under 35 U.S.C. §102(b) as allegedly being anticipated by Clapper. The Examiner states that Clapper teaches culturing endothelial cells in culture plates in which polymers with immobilized peptides are placed. He also states that the cells adhere to the immobilized peptides, and the cells' growth is enhanced. Moreover, he states that all of the peptides of Clapper comprise at least one of the structures recited in claim 1; and that they inherently have the functional properties of Applicants' peptides.

As described above, claim 1 as amended is directed to a cell culture system comprising a pentameric peptide according to at least one of structures (a)-(e). Moreover, claim 1 as amended recites that the peptide is free or noncovalently immobilized to a cell culture surface. Neither of these features are taught nor suggested by Clapper.

Instead, Clapper is directed to a reagent comprising a polymeric backbone bearing one or more photoreactive moieties and one or more bioactive groups, such as peptides. None of the peptides disclosed by Clapper are pentamers. For example, in the table that spans columns 13 and 14, the peptides range in length from 11-mers to a 16-mer. As described above, such long peptides are susceptible to degradation during cell culture and to the proteolytic action of the cultured cells themselves.

Moreover, in contrast to the present invention, in Clapper it was necessary to covalently photoimmobilize the peptides to a surface (e.g., polystyrene) in order for the peptide polymers to enhance cell attachment and cell growth activity sufficiently. In particular, Clapper's adsorbed peptide reagent resulted in an insufficient amount of cell attachment and cell growth activity. See, for example, from column 17, line 9 to column 19, line 28 of Clapper.

Applicants invention presents significant advantages over Clapper in that the small 5-mer peptides are resistant to degradation, resistant to the desorptive effect, and do not require covalent immobilization to a cell culture surface.

In view of the amendment to claim 1 and the remarks presented herewith, Applicants respectfully submit that claim 1 and the claims depending therefrom are patentable over Clapper.

With respect to the remaining rejections, claim 42 has been canceled, thereby obviating this rejection. Claims 44 and 48 have been amended to recite the peptides listed in original claim 30, which are not disclosed by Clapper. Therefore, Applicants submit that claims 44 and 48 are also patentable over Clapper.

Therefore, Applicants respectfully request withdrawal of these rejections.

U.S. Patent No. 5,834,029 to Bellamkonda, et al (hereinafter Bellamkonda)

The Examiner has rejected claims 1, 2, 5-17, 19-21, 33, 36, 37, 42-44 and 48 under 35 U.S.C. §102(b) as allegedly being anticipated by Bellamkonda. In particular, the Examiner states that Bellamkonda teaches nerve guide channels including a hydrogel extracellular matrix to which a peptide comprising the partial sequence, IKVAV, is attached. He also states that, in view of similarity in structure between the peptides of Bellamkonda and the instant claimed peptides, inherently the peptides of Bellamkonda will have the same functional properties as those of Applicants' peptides.

Bellamkonda is directed to a nerve guidance channel, which includes a three-dimensional hydrogel extracellular matrix derivatized with a cell adhesive peptide fragment. The peptide fragment can contain the sequence IKVAV, and is covalently immobilized to the matrix. The matrix acts as a support for nerve regeneration, whereby host cells infiltrate the matrix.

In contrast to the invention as now recited in claims 1 and 20, Bellamkonda does not disclose a pentameric peptide for use in a cell culture system. Bellamkonda, at best, teaches that a peptide for use in a nerve guidance channel can contain the sequence IKVAV. However, SEQ ID NO: 3 is the only disclosed peptide containing this sequence, and it is a 19-mer. As noted above, such long peptides are highly susceptible to degradation in cell culture systems.

Also, amended claims 1 and 20 recite that the peptide is free or non-covalently immobilized to a cell culture surface. Similarly, in claims 33 and 36, the peptide is non-covalently attached or nonspecifically adsorbed to a cell culture surface. In contrast, Bellamkonda's peptides are covalently immobilized to the matrix.

Applicants invention presents significant advantages over Bellamkonda in that the small 5-mer peptides are resistant to degradation, resistant to the desorptive effect, and do not require covalent immobilization to a cell culture surface.

In view of the amendment to claim 1 and the remarks presented herewith, Applicants respectfully submit that claim 1, and the claims depending therefrom, are patentable over Bellamkonda.

Regarding the remaining rejections, claims 42 and 43 have been canceled, thereby obviating these rejections. Claims 44 and 48 have been amended to recite the peptides listed in original claim 30, which are not disclosed by Bellamkonda. Therefore, Applicants submit that claims 44 and 48 are also patentable over Bellamkonda.

Therefore, Applicants respectfully request withdrawal of these rejections.

Rejections under 35 U.S.C. §102 (a)

Tong, et al. (hereinafter Tong)

The Examiner has rejected claims 1, 2, 5-13, 19-21, 33, 36, 37, 42, 44 and 48 under 35 U.S.C. §102(a) as allegedly being anticipated by Tong, et al (Biomaterials 22 (2001) 1029-1034). The Examiner states that Tong teaches neurons cultured on a surface comprising an FEP film modified with the peptide SIKVAV, and that this peptide comprises the elected structure xkxxx. He also states that Tong's peptide will inherently possess the same functional properties as those of Applicants' claimed peptides.

Applicants' amended claims recite a pentameric peptide, which is not anticipated by the 6-mer of Tong.

Moreover, amended claims 1 and 20 recite that the peptide is free or non-covalently immobilized to a cell culture surface. Similarly, in claims 33 and 36, the peptide is non-covalently attached or nonspecifically adsorbed to a cell culture surface. In contrast, Tong's peptides are covalently attached to a cell culture surface, which as discussed in Applicant's

background has significant disadvantages. See, paragraph [0010]. For example, a disadvantage is that the surface must first be activated before the surface can be derivatized with a peptide. The activating process can be lengthy in time and involve toxic reagents, requiring thorough washing of the surface prior to modification with the peptide and prior to culturing of the cells on the derivatized surface. Also, the efficiency of peptide immobilization is highly dependent on the prior polymer derivatization process. Finally, the final range of peptide concentration and orientation on the surface are restricted.

In view of the amendments and remarks presented herewith, Applicants submit that claims 1, 20, 33 and 36, and the claims depending therefrom, are patentable over the Tong reference.

Regarding the remaining rejections, claim 42 has been canceled, thereby obviating this rejection. Moreover, claims 44 and 48 have been amended to recite the peptides listed in original claim 30, which are not disclosed by Tong. Therefore, Applicants submit that claims 44 and 48 are also patentable over Tong.

Therefore, Applicants respectfully request withdrawal of these rejections.

U.S. Patent No. 6,759,510

Finally, the Examiner has indicated that the '510 patent would form the basis for a rejection of claims 1, 2, 5-7, 10-12, 19 and 14 under 35 U.S.C. §102(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. §102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made.

Applicants do not believe that the '510 patent qualifies as prior art under 35 U.S.C. §102(e), (f) or (g). See, for example, Applicants arguments under 35 U.S.C. §102(e) rejections regarding the '510 patent.

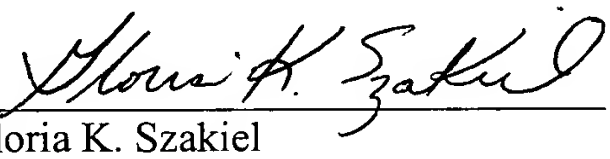
However, in the event that the Examiner maintains that the '510 patent is a proper basis for the 35 U.S.C. §102(e) rejection, Applicants are prepared to submit a showing that the allegedly conflicting inventions were commonly owned at the time the invention in this application was made.

Summary

In view of the amendments and remarks presented herewith, Applicants submit that the claims are allowable in form and patentably distinct from the prior art. Allowance is therefore respectfully solicited.

Should the Examiner have any questions regarding the present invention or remarks relating thereto, contacting the undersigned by telephone is encouraged.

Respectfully submitted,



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Amendments to the Drawings:

Please delete Figure 1, and replace it with the replacement drawing sheet submitted herewith. In particular, the absorbance value of 1.80 for h-collagen I in replacement Figure 1 has been deleted.